



AF/1632
USSN: 09/464,795
Dkt. No.: PXE-007.US
9400-0002

PATENT

CERTIFICATE OF MAILING PURSUANT TO 37 CFR § 1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Appeal Brief, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on June 1, 2006.

6/1/06
Date

Michelle Hobson
Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

ZHANG et al.

Serial No.: 09/464,795

Filing Date: December 16, 1999

Title: NON-INVASIVE EVALUATION OF
PHYSIOLOGICAL RESPONSE IN A
MAMMAL

Examiner: Anne Marie Falk

Group Art Unit: 1632

Confirmation No.: 8087

Customer No.: 20855

TRANSMITTAL

Mail Stop Appeal Brief
Commissioner for Patents
P. O. Box 1450
Arlington, VA 22313

Dear Sir:

Transmitted herewith for filing are the following documents in the above patent application.

- X Appeal Brief (17 pages) with attached Claims Appendix (4 pages), Evidence Appendix (1 page) and Related Proceedings Appendix (1 page)
- X A return receipt postcard

The fee is calculated as follows:

	NO. OF CLAIMS	CLAIMS PREVIOUSLY PAID FOR	EXTRA CLAIMS	RATE	FEE
Total Claims	10	- 64	0	x \$50.00	\$0
Independent Claims	1	- 7	0	x \$200.00	\$0
Multiple dependent claims not previously presented add \$360.00					\$0
Total Amendment Fee					\$0
Petition for Extension of Time Fee					\$0
Fee for filing an Appeal Brief					\$500.00
TOTAL FEE DUE					\$500.00

X A check in the amount of \$500.00.

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 18-1648.

Respectfully submitted,

Date: June 1, 2006

By: 
Dahna S. Pasternak
Registration No. 41,411

ROBINS & PASTERNAK LLP
1731 Embarcadero Road, Suite 230
Palo Alto, CA 94303
Tel. (650) 493-3400
Fax. (650) 493-3440



USSN 09/464,795
9400-0002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

ZHANG et al.

Serial No.: 09/464,795

Filing Date: December 16, 1999

Title: NON-INVASIVE EVALUATION OF
PHYSIOLOGICAL RESPONSE IN A MAMMAL

Examiner: Anne Marie Falk

Group Art Unit: 1632

Confirmation No.: 8087

Customer No.: 20855

APPEAL BRIEF

ROBINS & PASTERNAK LLP
1731 Embarcadero Road
Suite 230
Palo Alto, CA 94303

Attorney for Appellant

USSN 09/464,795
9400-0002



TABLE OF CONTENTS

INTRODUCTION	1
I. REAL PARTY IN INTEREST.....	2
II. RELATED APPEALS AND INTERFERENCES.....	2
III. STATUS OF THE CLAIMS	2
IV. STATUS OF THE AMENDMENTS	2
V. SUMMARY OF THE CLAIMED SUBJECT MATTER.....	2
VI. GROUNDS OF REJECTION	5
VII. ARGUMENTS.....	5
1. The Appealed Claims Have Patentable Utility.....	5
(a) Transgenic Mice Containing Reporter Constructs “Recapitulate Native Gene Expression”	6
(b) The Actual “Asserted” Utility is Well-Established, Substantial and Specific	7
2. The As-Filed Specification Describes the Subject Matter of the Appealed Claims	8
3. The As-Filed Specification Enables the Subject Matter of the Appealed Claims	11
CONCLUSION.....	15
CLAIMS APPENIDIX	
EVIDENCE APPENDIX	
RELATED PROCEEDINGS APPENDIX	

USSN 09/464,795
9400-0002



I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Alexandria, VA 22313 on **June 1, 2006**.

6/1/06 Michelle Hobson
Date Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

ZHANG et al.

Serial No.: 09/464,795

Filing Date: December 16, 1999

Title: NON-INVASIVE EVALUATION OF
PHYSIOLOGICAL RESPONSE IN A MAMMAL

Examiner: Anne Marie Falk

Group Art Unit: 1632

Confirmation No.: 8087

Customer No.: 20855

APPEAL BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
Alexandria, VA 22313

Sir:

INTRODUCTION

Appellant submits one copy of this brief on appeal in accordance with Section 41.37 (69 Fed. Reg. 49962, Aug 2004). All claims were finally rejected under 35 U.S.C. §§102 and 112, 1st paragraph, in a Final Office Action mailed February 8, 2006. A Notice of Appeal was received by the USPTO on May 3, 2006, making a Brief on Appeal due July 3, 2006.

Accordingly, this Appeal Brief is timely filed.

06/07/2006 NNGUYEN1 00000063 09464795

01 FC:1402

500.00 OP

I. REAL PARTY IN INTEREST

Xenogen Corporation, the assignee of record of the above-referenced patent application, is the real party in interest in this matter.

II. RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any related appeals, interferences or judicial proceedings.

III. STATUS OF THE CLAIMS

Claims 38, 40, 41, 43, 45, 46, 49 and 65-68 are currently pending in the above-referenced case (hereinafter "the application") as shown in the Claims Appendix. Claims 1-37, 39, 42, 44, 50-64 and 69-80 were canceled. Therefore, pending claims 38, 40, 41, 43, 45, 46, 49 and 65-68 are appealed and stand rejected under 35 U.S.C. § 101 and 35 U.S.C. § 112, 1st paragraph (written description and enablement).

IV. STATUS OF THE AMENDMENTS

In response to the Examiner's Final Office Action mailed October 10, 2005, Appellants filed a Response with arguments and amendments to claim 38. An Advisory Action was mailed on April 28, 2006 indicating that the amendment would be entered and overcame the rejections under 35 U.S.C. § 112, 2nd paragraph. Thus, all claims on appeal are rejected under 35 U.S.C. § 101 and 35 U.S.C. § 112, 1st paragraph (written description and enablement) for the reasons set forth in the Final Office Action and Advisory Action.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The claimed subject matter is drawn to transgenic mice comprising multiple light-emitting reporter constructs (page 4, lines 24-26) and to non-invasive methods of using these transgenic mice, for example to determine the effect of analyte on the promoters of the reporter

constructs (page 5, lines 7-19); to detect a level of expression in response to an analyte (page 5, line 20-22); and/or to screen a selected analyte (page 5, lines 17-19).

In particular, independent claim 38 is drawn to a transgenic mouse comprising a panel of expression cassettes (page 4, lines 24-26). The transgenic mouse is produced by a method comprising the steps of introducing, into a mouse at an embryonic stage (page 60, lines 2-7; page 65), first and second expression cassettes (page 4, lines 1-5). The first expression cassette comprises a first promoter operably linked to sequences encoding a first light generating polypeptide (page 4, lines 2-3) and the first promoter is derived from a first stress-inducible gene (page 4, line 17). The second expression cassette comprises a second promoter operably linked to sequences encoding a second light generating polypeptide (page 4, lines 4-5). The second promoter is derived from a different stress-inducible gene than the first promoter is derived from (page 4, lines 6-8 and line 17).

Dependent claim 65 is drawn to the transgenic mouse of claim 38, and further specifies that the method comprises introducing a third expression cassette (page 4, line 11) comprising a promoter derived from a third stress-inducible gene (page 4, line 17) into a mouse at an embryonic stage, said third promoter operably linked to sequences encoding a third light generating polypeptide and said third promoter derived from a different stress-inducible gene than said first and second promoters (page 4, line 11-17).

Dependent claim 66 is drawn to the transgenic mouse of claim 65, wherein (i) said first, second, and third promoters are each derived from a different gene (page 4, line 6-8), and (ii) said first, second, and third light generating polypeptides produce the same color of light (page 4, lines 6-9). Dependent claim 67 is drawn to the transgenic mouse of claim 65, wherein (i) said first, second, and third promoters are each derived from a different gene (page 4, line 6-8), and (ii) at least two of said first, second, and third light generating polypeptides produce different colors of light (page 4, lines 6-8).

Dependent claim 68 is drawn to the transgenic mouse of claim 65, and further indicates that the panel of expression cassettes comprises additional expression cassettes (page 4, lines 11-12), wherein each expression cassette comprises a promoter derived from a different stress-

inducible gene, said promoter operably linked to sequences encoding a light generating polypeptide.

Dependent claim 40 is drawn to a method of determining the effect of an analyte on gene expression mediated by promoters derived from stress-inducible genes, by administering the analyte to a living transgenic mouse of independent claim 38 under conditions that permit light generation mediated by said light generating polypeptide in the transgenic mouse, and determining the effect of the analyte on expression of the light generating polypeptide in a living transgenic mouse wherein said expression is mediated by at least one of the promoters (page 5, lines 7-19).

Dependent claim 41 specifies that the conditions that permit light generation mediated by the light generating polypeptide includes administering, to the transgenic mouse, at least one substrate for the light generating polypeptide.

Dependent claim 45 is drawn to a noninvasive method for detecting a level of expression in response to an analyte, wherein said expression is (i) mediated by promoters derived from stress-inducible genes, and (ii) in a living transgenic mouse (page 5, lines 20-22). The method comprises (a) administering the analyte to a living transgenic mouse of claim 38, wherein administering of said analyte is carried out under conditions that permit light generation mediated by said light generating polypeptide (page 5, line 24-25); (b) placing the transgenic mouse within a detection field of a photo detector device (page 5, lines 25-26); (c) maintaining the transgenic mouse in the detection field of the device (page 5, lines 26-27); and (d) during said maintaining, measuring photon emission from the transgenic mouse with the photo detector device to detect the level of expression of the light generating polypeptide in the living transgenic mouse wherein said expression is mediated by at least one of the promoters (page 5, lines 26-29). Dependent claim 46 specifies that steps (b) through (d) are repeated at selected intervals such that changes in the level of the light emission in the transgenic mouse are detected over time (page 5, lines 29 to page 6, line 3).

Dependent claim 49 is drawn to a method of providing a transgenic mouse suitable for screening a selected analyte, comprising generating a transgenic mouse of claim 38, and

providing said transgenic mouse or progeny thereof for use in screening a selected analyte (page 5, lines 17-19).

VI. GROUNDS OF REJECTION

1. Claims 38, 40, 41, 43, 45, 46, 49 and 65-68 stand rejected under 35 U.S.C. § 101 as allegedly lacking patentable utility.

2. Claims 38, 40, 41, 43, 45, 46, 49 and 65-68 stand rejected under 35 U.S.C. § 112, 1st paragraph as allegedly not adequately described by the specification as filed.

3. Claims 38, 40, 41, 43, 45, 46, 49 and 65-68 stand rejected under 35 U.S.C. § 112, 1st paragraph as allegedly not enabled by the specification as filed.

VII. ARGUMENTS

1. The Appealed Claims Have Patentable Utility

Claims 38, 40, 41, 43, 45, 46, 49 and 65-68 remain rejected under 35 U.S.C. § 101 as allegedly lacking patentable utility. (Advisory Action, page 2). In support of this rejection, the Advisory Action states:

With regard to the utility rejection, Applicants assert, at pages 5-6 of the response, that the Examiner acknowledges there is well-established utility set forth in the specification. On the contrary, the Examiner alerted Applicant that the utility they were referring to was actually an **asserted** utility. ... An asserted utility should be not be confused with a well-established utility. ... An asserted utility must be specific to the claimed subject matter. The specification is clear that the intention is to create a construct and experimental system that recapitulates **native gene expression**, not gene expression in an artificial context. The specification does not provide specific guidance for creating constructs, within the scope of the claims that have this utility.¹

¹ Advisory Action, page 2, emphasis in original

Appellants reiterate the evidence of record establishes that the as-filed specification sets forth patentable utilities (well-established, credible and substantial) for the particularly claimed subject matter.

(a) Transgenic Mice Containing Reporter Constructs “Recapitulate Native Gene Expression”

The Examiner’s utility rejection is based on the erroneous assertion that the asserted utility of “recapitulating native gene expression” is not supported in the as-filed specification.

In fact, “recapitulating native gene expression” is simply another way of phrasing the well-established use of reporter constructs to analyze gene expression. At the time of filing (and to this day), reporter constructs containing a promoter of a gene of interest operably linked to a reporter sequence were the preferred way of “recapitulating native gene expression,” both *in vivo* and *in vitro*. The well-established use of reporter constructs to recapitulate native gene expression is described in the as-filed specification:

Cardiovascular biology and diseases have been investigated in Tg mouse models using tissue-specific promoters [citations omitted] and regulation of insulin-responsive glucose transporter GLUT4 and Apo A-I genes have also been studied in models of diabetes, obesity [citation omitted] and coronary artery disease [citations omitted].

Photoproteins as biological labels have been used for more than a decade for the study of gene expression in cell culture or using excised tissue [citations omitted]. Low-light imaging of internal bioluminescent signals has been used to study temporal and spatial gene regulation in relatively thin or nearly transparent organisms [citations omitted]. External detection of internal light penetrating the opaque tissues has been described [citation omitted].²

Thus, the asserted utility (non-invasive *in vivo* analysis of gene expression using animals comprising multiple reporter constructs) was well-established, substantial and credible for single constructs. As such, it is utterly irrelevant whether the “asserted” utility is phrased as “recapitulating native gene expression;” “analysis of gene expression;” or “use of reporter

² Page 3, lines 2-33 of the application; *see, also*; page 22, lines 2-12 of the application

constructs to characterize the effect of an analyte on a particular promoter.” The skilled artisan would view these terms as interchangeable and, moreover, would recognize the well-established, credible, substantial and specific utilities disclosed in the as-filed specification.

(b) The Actual “Asserted” Utility is Well-Established, Substantial and Specific

Moreover, as repeatedly noted, a utility rejection should not be imposed where there is a well-established utility and/or where there is one credible utility (*see*, M.P.E.P. § 2107, emphasis added):

If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. ...

(1) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

... An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement.

In the case on appeal, it was well-established at the time of filing that reporter constructs comprising a promoter operably linked to a reporter sequence “recapitulate native gene expression” (*i.e.*, via analysis of reporter gene expression which is indicative of the effect on the promoter operably linked to the reporter). Using a single reporter construct was (and remains) the preferred way to analyze gene expression which, in turn, facilitates, for example, drug screening, both *in vitro* and *in vivo*.³ This preferred method of promoter analysis (or, put in the Examiner’s terms, the preferred method of recapitulating native gene expression) has a well-established utility and, accordingly, the rejection cannot stand.

³ *See, e.g.*, Background and page 60, line 29 to page 61, line 6 of the application, describing the well known monitoring of expression of lux/luc reporter genes using non-invasive whole animal imaging and citing U.S. Patent No. 5,650,135.

In sum, the evidence of record demonstrates that reporter constructs recapitulate native gene expression by virtue of the promoter selected. Since this is a well-established, specific, credible and substantial utility for the claimed subject matter, Appellants submit that withdrawal of this rejection is in order.

2. The As-Filed Specification Describes the Subject Matter of the Appealed Claims

Claims 38, 40, 41, 43, 45, 46, 49 and 65-68 also remain rejected under 35 U.S.C. § 112 as allegedly not adequately described by the as-filed specification. (Advisory Action, page 3). In support of this rejection, the Advisory Action states:

The [written description] rejection of record is grounded in the failure of the specification to describe those constructs that will provide for **native gene expression** and thereby be representative of native gene expression, such that the effect of an analyte on the construct will be representative of the effect of the analyte on the promoter (and its elements) in its native context. ... the specification has not described those constructs that will provide for **native gene expression**.⁴

For the reasons of record and noted above, Appellants submit that there is ample description in the specification, in view of what was well known in the art, regarding how reporter constructs as used in the claimed animals and methods allow for the screening of analytes via their effect on the promoter of the reporter constructs.

It is axiomatic that a patent specification “need not teach, and preferably omits, what is well known in the art.” See, *Spectra-Physics, Inc. v. Coherent, Inc.* 3 USPQ2d 1737, 1743 (Fed. Cir. 1987); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). Thus, there is no requirement to describe that which is well-known at the time of filing. Indeed, this has recently been reiterated by the Federal Circuit in *Capon v. Eshhar* 76 USPQ2d 1078 (CA FC 2005):

⁴ Advisory Action, page 3, emphasis in original

None of the cases to which the Board attributes the requirement of total DNA re-analysis, *i.e.*, *Regents v. Lilly*, *Fiers v. Revel*, *Amgen*, or *Enzo Biochem*, require a re-description of what was already known.

It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *See In re Angstadt*, 537 F.2d 498, 504 [190 USPQ 214] (CCPA 1976) (“The examples, both operative and inoperative, are the best guidance this art permits, as far as we can conclude from the record”). While the Board is correct that a generic invention requires adequate support, the sufficiency of the support must be determined in the particular case. ...

In the case on appeal, the state of the art and as-filed specification clearly establish that “recapitulating native gene expression” in transgenic animals by introducing a reporter construct comprising a selected promoter operably linked to a reporter sequence was well known at the time of filing:

A wide range of Tg mice that employ reporter constructs have been developed and tested. For example, Tg mice containing the viral long terminal repeat (LTR) promoter fusions have been used to study the range of tissues and cells types that are capable of supporting HTLV-1 expression and the development of neurofibromatosis-like tumors associated with HTLV-1 retrovirus ... [citations omitted]. Cardiovascular biology and diseases have been investigated in Tg mouse models using tissue-specific promoters [citations omitted], and regulation of insulin-responsive glucose transporter GLUT4 and Apo A-I genes have also been studied in models of diabetes, obesity [citation omitted] and coronary artery disease [citation omitted].

Photoproteins as biological labels have been used for more than a decade for the study of gene expression in cell culture or using excised tissue...⁵ ...

The monitoring of *lux/luc* reporter genes using non-invasive whole animal imaging has been described [citing U.S. Patent No. 5,650,135 and other citations].⁶

⁵ See, *e.g.*, page 2, line 29 to page 3, line 12 of the application

⁶ See, *e.g.*, page 60, line 29 to page 61, line 6 of the application

Thus, although not required because it is not new, the as-filed specification describes “recapitulating native gene expression” using a reporter construct was well known as well as how to make transgenic mice comprising these reporter constructs.

Furthermore, Appellants have described what *is* new, namely using panels of multiple reporter constructs in a single transgenic animal to allow analysis of multiple stress-inducible genes in a single live animal model:

The present invention provides a powerful new tool for analyzing biochemical pathways and physiological functions (*e.g.*, toxicity, inflammation, pain, development, oncogenesis, apoptosis, etc.) both *in vivo* and *in vitro*. Using this unique approach, termed *in vivo* differential display (IVDD), gene expression in living animals can be readily studied. IVDD has many uses, including, but certainly not limited to, drug testing and development and toxicological testing for chemicals.

During virtually all non-normal physiological states, organisms activate (induce) specific **genes** or groups of **genes**. Thus, infectious agents, pathological conditions, environment and/or toxic stimuli may induce the expression of certain **genes** associated with a particular biochemical pathway of physiological condition.⁷ ...

The control elements of the **genes** of interest are operably linked to reporter **genes** to create chimeric **genes** that [are] used to generate transgenic animals (*e.g.*, mice). These transgenic animals can then serve as test animals for example, for toxicology or stress testing. Induction of expression of these **genes** can be evaluated using non-invasive imaging.⁸

In view of this clear description of the claimed subject matter and the axiomatic rule that it is **not** required that animals comprising multiple reporter constructs be exemplified in order to satisfy the written description requirement, it is plain that the disclosure as a whole, including the well-known and the new, amply establishes that the written description requirement in the case on appeal has been satisfied.

Appellants have shown possession of animals and methods that provide an *in vivo* screening method using multiple reporter constructs, and, accordingly, the written description requirement of 35 U.S.C. § 112, first paragraph has been satisfied.

⁷ Page 22, lines 3-12 of as-filed specification, emphasis added to show multiple reporter constructs employed

⁸ Page 23, lines 22-25 of as filed specification, emphasis added to show multiple reporter constructs employed

3. The As-Filed Specification Enables the Subject Matter of the Appealed Claims

Claims 38, 40, 41, 43, 45, 46, 49 and 65-68 also remain rejected under 35 U.S.C. § 112 as allegedly not enabled by the as-filed specification. (Advisory Action, page 3). In support of this rejection, the Advisory Action states:

...the existence of transgenic mice expressing light generating proteins is not sufficient to enable the claimed invention because the **claimed** invention requires the generation of transgenic mice having promoters that regulate expression of the light generating proteins in a manner that is **predictive** of native gene expression (the only asserted utility for the claimed transgenic mouse). ... The specification fails to enable the identification of such promoter portions that the native context is retained when the promoter is truncated and inserted into an expression cassette, which is then inserted into the genome of a mouse (in a new genetic context).⁹

The rejection is based on multiple unsupportable assumptions.

First, the assumption that reporter constructs containing promoters of known genes operably linked to reporter molecules are not predictive of native gene expression is in error. Reporter molecules as claimed were known to predict native gene expression, both *in vivo* and *in vivo*:

During virtually all non-normal physiological states, organisms activate (induce) specific genes or groups of genes.¹⁰

In one aspect of the invention, reporter gene expression cassettes are constructed using control elements selected from a gene or group of genes whose expression is known to be associated with a particular biochemical pathway or physiological function. For example, the control elements may be stress-inducible control elements selected from a gene or group of genes associated with cellular stress or toxicity. **Thus, toxicity can be monitored *in vivo* by analyzing expression of the reporter gene.** [T]he regulatory (or control) sequences confer the responsiveness to the construct, i.e., the promoter taken as a whole functions like a promoter derived from a selected gene.¹¹

⁹ Advisory Action, page 3, emphasis in original

¹⁰ Page 22, lines 9-10 of the application

¹¹ Page 33, lines 5-10 and lines 23-25 of the application, emphasis added

Second, the allegation that the specification is required to “enable” identification of promoter portions is unsupported. The specification clearly teaches that many stress-related promoters were well known at the time of filing and there are pages and pages of description and references regarding these promoters and portions thereof (including, for example, CREs) that retain their ability to predict native gene expression when truncated:

Many stress-inducible genes have been identified, sequenced and analyzed. Information about stress-related control elements is widely available. In the practice of the present invention, stress-related control elements are selected, and operably linked to a reporter gene coding sequence, which results in the generation of chimeric genes where the reporter gene coding sequence (for example, sequences encoding a light generating polypeptide such as luciferase) are subject to the regulation provided by the stress-related control elements.¹²

Each gene is controlled by a unique promoter. However, genes that respond to a particular stimuli (*e.g.*, stress, infection) can contain within their promoters, a common response element (CRE) or, associated with their promoters, regulatory or control sequences involved with regulation of expression of the gene (*e.g.*, induction or repression). ... CREs (or other regulatory or control elements associated with a selected gene) can be isolated [citations omitted] and operably linked to a minimal promoter and a reporter gene.¹³

Third, contrary to the Examiner’s allegations, the specification teaches how to identify promoters and functional portions thereof from any gene:

Genes, and promoters from these genes, that are induced by the aforementioned stimuli can be identified as described herein. For example, subtractive hybridization can be used to determine which transcripts are activated (or overexpressed) when the cells or animals are exposed to the stimuli of interest.¹⁴

¹² Page 35, lines 12-17 of the application; *see, also*, pages 35 to 41 of the application and references cited therein regarding stress-inducible promoters and portions thereof

¹³ Page 33, lines 14-25 of the application

¹⁴ Page 22, lines 13-16 of the application

Fourth, not only does the specification teach both that stress-inducible promoters (and portions thereof) were known at the time of filing and how to identify additional promoters (and regions thereof), the specification clearly defines the claim term “operably linked” such that the promoter of the reporter construct is required to perform its usual (native) function, *i.e.*, recapitulate native gene expression:

“Operably linked” refers to an arrangement of elements wherein the components so described are configured so as to perform their usual function. Thus, a given promoter that is operably linked to a coding sequence (e.g., a reporter expression cassette) is capable of effecting the expression of the coding sequence when the proper enzymes are present.¹⁵

The evidence of record clearly establishes that recapitulating native gene expression in a transgenic mouse comprising a single reporter construct (including a light-generating reporter) was known. Thus, the skilled artisan would expect that multiple of such constructs would also function as claimed, in view of the disclosure in the as-filed specification.

As set forth in the seminal case of *In re Marzocchi*, 439 F.2d, 220, 223, 169 USPQ 367, 369 (CCPA 1971), a patent application is presumptively enabled when filed:

[a]s a matter of Patent Office practice ... a specification .. must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Moreover,

it is incumbent upon the Patent Office, whenever a rejection on [grounds of enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

¹⁵ See, page 12, line 30 to page 13, line 1 of the application

439 F.2d at 224, 169 USPQ at 369-370. Indeed, as pointed in the Patent Office's own Training Manual on Enablement (1993, citing *In re Wright*, 999 F.2d 1557, 1561-1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993), "the case law makes clear that properly reasoned and supported statements explaining any failure to comply with section 112 are a requirement to support a rejection."

In the case on appeal, the Examiner has not properly set forth why the teachings of the specification do not enable the skilled artisan to make and use the claimed subject matter. The specification establishes that single reporter constructs introduced to make transgenic animals can recapitulate native gene expression *in vivo*. The Office has not provided any reason to doubt that the multiple reporter constructs are operative.

The Office has not met its burden of overcoming the evidence of record which demonstrates that the specification enables the pending claims throughout their scope. As such, the rejection cannot stand.


USSN 09/464,795
9400-0002

CONCLUSION

For the reasons stated above, Appellant respectfully submits that the specification adequately describes the pending claims and that the pending claims are patentable over the art cited by the Examiner. Accordingly, Appellant requests that the rejections of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: June 1, 2006

By: 
Dahna S. Pasternak
Registration No. 41,411
Attorney for Appellant

ROBINS & PASTERNAK LLP
1731 Embarcadero Road, Suite 230
Palo Alto, CA 94303
Telephone: (650) 493-3400
Facsimile: (650) 493-3440

USSN 09/464,795
9400-0002

CLAIMS APPENDIX

USSN 09/464,795
9400-0002



CLAIMS ON APPEAL

1-37. (canceled)

38. (previously presented): A transgenic mouse comprising a panel of expression cassettes, said transgenic mouse produced by a method comprising the steps of

introducing a first expression cassette comprising a first promoter derived from a first stress-inducible gene into a mouse at an embryonic stage, said promoter operably linked to sequences encoding a first light generating polypeptide, and

introducing a second expression cassette comprising a second promoter derived from a second stress-inducible gene into said mouse at an embryonic stage, said promoter operably linked to sequences encoding a second light generating polypeptide and said second promoter derived from a different stress-inducible gene than said first promoter.

39. (canceled)

40. (previously presented): A method of determining the effect of an analyte on gene expression mediated by promoters derived from stress-inducible genes, wherein said expression is in a living transgenic mouse, said method comprising

administering the analyte to a living transgenic mouse of claim 38, wherein administering of said analyte is carried out under conditions that permit light generation mediated by said light generating polypeptide in the transgenic mouse,

determining the effect of the analyte on expression of the light generating polypeptide in a living transgenic mouse wherein said expression is mediated by at least one of the promoters.

41. (previously presented): The method of claim 40, wherein said conditions that permit light generation mediated by the light generating polypeptide includes administering, to the transgenic mouse, at least one substrate for the light generating polypeptide.

USSN 09/464,795
9400-0002



42-44. (canceled)

45. (previously presented): A noninvasive method for detecting a level of expression in response to an analyte, wherein said expression is (i) mediated by promoters derived from stress-inducible genes, and (ii) in a living transgenic mouse, said method comprising

(a) administering the analyte to a living transgenic mouse of claim 38, wherein administering of said analyte is carried out under conditions that permit light generation mediated by said light generating polypeptide,

(b) placing the transgenic mouse within a detection field of a photo detector device,

(c) maintaining the transgenic mouse in the detection field of the device, and

(d) during said maintaining, measuring photon emission from the transgenic mouse with the photo detector device to detect the level of expression of the light generating polypeptide in the living transgenic mouse wherein said expression is mediated by at least one of the promoters.

46. (previously presented): The method of claim 45, further comprising, (e) repeating steps (b) through (d) at selected intervals, wherein said repeating is effective to detect changes in the level of the light emission in the transgenic mouse over time.

47-48. (canceled)

49. (previously presented): A method of providing a transgenic mouse suitable for screening a selected analyte, comprising
generating a transgenic mouse of claim 38, and

providing said transgenic mouse or progeny thereof for use in screening a selected analyte.

50-64. (canceled)

65. (previously presented): The transgenic mouse of claim 38, wherein the method further comprises

introducing a third expression cassette comprising a promoter derived from a third stress-inducible gene into a mouse at an embryonic stage, said third promoter operably linked to sequences encoding a third light generating polypeptide and said third promoter derived from a different stress-inducible gene than said first and second promoters.

66. (previously presented): The transgenic mouse of claim 65, wherein (i) said first, second, and third promoters are each derived from a different gene, and (ii) said first, second, and third light generating polypeptides produce the same color of light.

67. (previously presented): The transgenic mouse of claim 65, wherein (i) said first, second, and third promoters are each derived from a different gene, and (ii) at least two of said first, second, and third light generating polypeptides produce different colors of light.

68. (previously presented): The transgenic mouse of claim 65, said panel further comprising additional expression cassettes, wherein each expression cassette comprises a promoter derived from a different stress-inducible gene, said promoter operably linked to sequences encoding a light generating polypeptide.

69-80. (canceled)

USSN 09/464,795
9400-0002

EVIDENCE APPENDIX

No documents are attached to this Evidence Appendix.

USSN 09/464,795
9400-0002



RELATED PROCEEDINGS APPENDIX

As noted above on page 2 of this Brief on Appeal Appellants are not aware of any related proceedings. In as much as no decisions have been rendered by a court or the Board in this related case, no documents are submitted with the Evidence Appendix.